REMARKS

Applicants respectfully request reconsideration of the present application and hereby traverse the outstanding rejections. The foregoing amendment is made without prejudice or disclaimer.

Disrupted Prosecution

With all due respect to the Office, applicants note for the record that the prosecution of the instant application has been hindered by having three different examiners sequentially examine the application. Applicants have flown from Europe twice to interview the application, have met each new examiner, thought they came to agreement with the Office, and followed-up with their representations at the interviews only to be confronted with a new examiner and different, conflicting rejections.

For example, the Interview Summary prepared by Examiner Connell relating to the Interview of 16 June 2000 stated:

> "Gall 96 teaches Ad5-Ad7 claims geared towards Ad7-Ad5. Claim 12 may be withdrawn from consideration and filed in a continuation. Table showing various serotypes may [be] entered via a 132 decl[aration]. Amendment distinguishes over the prior art for non cancelled claims."

Applicants understood from the interview that an amendment cancelling claim 12 would render the remaining claims free of prior art. In an Amendment filed on 1 August 2000, applicants canceled claims 4 through 8 and 12 without prejudice or disclaimer and amended claims 1, 2, 9, and 10 to make those claims more definite, as per the interview. It was applicants' understanding that the amendment would result in the allowance of claims 1 through 3 and 9 through 11.

However, subsequent to the 16 June 2000 interview, responsibility for the present application was transferred to another examiner who did not allow the non-cancelled claims but instead rejected the application based on work she was involved with at her former employer.

Again, applicants traveled to the United States, met with the examiner, agreed to a new claim structure to overcome the art of record, which was ultimately presented in the claims 13 through 32. Now, however, the very claims agreed on have been withdrawn by still another new examiner.

Applicants understand that the present Examiner had nothing to do with the earlier ones but would still like to express their frustration with the entire process.

Information Disclosure Statement

The Office indicates in the outstanding Final Office Action that no evidence of record exists indicating that the Office has received the form PTO-1449 filed by applicants on 26 January 2001, concurrently with applicants' Second Supplemental Information Disclosure Statement ("SSIDS"). Therefore, the Office advises, applicants' statements concerning such references cannot be properly evaluated nor can the Office consider such references.

Applicants filed their SSIDS, including the form PTO-1449, via a Certificate of Mailing under 37 C.F.R. § 1.8(a), dated 24 January 2001. Applicants received a return postcard from the Office acknowledging receipt at the Office of Initial Patent Examination ("OIPE") on 26 January 2001, of, among other things, the SSIDS and accompanying form PTO-1449. A copy of the return postcard showing the 26 January 2001 OIPE date stamp is enclosed herewith. Also enclosed herewith is a copy of the SSIDS and form PTO-1449 filed on 26 January 2001.

Applicants respectfully request that the Office correct its records to reflect that the SSIDS and form PTO-1449 were filed on 26 January 2001. Applicants further request the Office to consider the references listed in the SSIDS and form PTO-1449 and applicants' previous statements relating to the same.

Claim Rejections - 35 U.S.C. § 112, second paragraph

Claims 1 through 3 and 11 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as their invention.

Claims 1 and 2, and claims 3 and 11 depending therefrom, stand rejected because the Office perceives it to be unclear what is meant by the phrase "at least a part of fiber protein is adapted to provide [or exhibit, cl. 2] . . . a desired tropism to a plurality of target cells in a host". Office Action, page 4. The Office asserts that it is unclear how "adapted" is defined and whether "adapted" is limited to human manipulation or also includes natural evolutionary adaptation. Id.

The specification makes clear that "adapted" refers to both human manipulation and natural evolution of the adenovirus coat proteins, including the hexon, penton, and fiber proteins. *See, e.g.,* Specification, page 5, line 18 to page 6, line 11; page 7, lines 5-10; page 8, line 9 to page 9, line 18; page 9, line 22 to page 10, line 13; page 18, lines 13-19; page 20, lines 11-28. "Adapted" refers to human manipulation of adenovirus coat proteins in the sense of replacing native adenovirus coat proteins with nonnative coat proteins. The nonnative coat proteins can be complete coat proteins from other adenovirus serotypes or they can be completely artificial coat proteins. *See, e.g.,* Specification page 9, line 22 to page 10, line 13. "Adapted" also refers to naturally occurring features of adenovirus coat proteins of different wild-type serotypes, such as

immunological properties and tissue tropisms, that have developed through evolutionary processes independent of human intervention. *See, e.g.,* Specification, page 3, line 27 to page 5, line 2.

"Adapted," as used in the present application, thus refers to the human manipulation involved in the creation of chimeric adenoviruses having nonnative coat proteins, but it also can refer to the naturally occurring characteristics of the various adenovirus wild-type serotypes. Applicants respectfully submit that the term "adapted," as used in rejected claims 1 and 2, and claims 3 and 11 depending therefrom, is not indefinite because it is used in a sense that is clearly defined in the specification and would be clearly understood by an ordinarily skilled artisan.

Claims 1 and 2, and claims 3 and 11 depending therefrom, further stand rejected because the Office perceives it be unclear what is meant by the terms "tropism" and "plurality" in the context of the claims. The ordinarily skilled artisan will immediately understand the term "tropism" in its plain and customary sense, namely, a receptor specificity or natural affinity for certain tissues in a host organism. And "plurality" plainly and customarily means more than one. When used together, as in claims 1 and 2, "tropism to a plurality of target cells" means a natural affinity for a particular tissue, which obviously comprises more than one cell. Applicants therefore respectfully assert that the terms "tropism" and "plurality" are not indefinite, particularly when used together, as in claims 1 and 2.

Claim 2, and claim 3 depending therefrom, further stand rejected because the Office perceives it to be indefinite what is meant by the term "functional part." The Office asserts that "any part of a fiber protein is 'functional' to the extent that it contributes one way or the other to the 'functional characteristics' of the fiber protein." Office Action, page 5. This point is well

taken.

Applicants propose to amend claim 2 to remove all occurrences of "functional." This amendment finds support in the specification at, for example, page 9 lines 18 to 27. Claim 2, as amended herein, now claims "a part of a fiber protein," which element, applicants respectfully aver, is clearly defined in the specification and satisfies the requirements of the second paragraph of Section 112. Withdrawal of this rejection therefore is respectfully solicited.

Claim Rejections - 35 U.S.C. § 102(e)

Notwithstanding the arguments presented in the Amendment dated 24 January 2001, claims 1-3 and 9-11 remain rejected under Section 102(e) as being assertedly anticipated by Crystal. The Office maintains that Crystal inherently teaches that "any adenoviral fiber protein within the context of [Crystal's] claimed invention has a particular tropism adapted for a particular plurality of target cells in a host . . . ." Office Action, page 8. Further, the Office asserts that applicants' declaration of Dr. Havenga under 37 C.F.R. § 1.132, filed on 1 August 2000, describing the range of antigenicities in humans of the various adenovirus serotypes, actually supports the contention that the adenoviral fiber proteins described in Crystal anticipate the adenoviral fiber proteins claimed by applicants. Office Action, pages 8-9. Applicants respectfully traverse the rejection.

First, applicants note that the relevant element in the present application to be compared with Crystal is: "at least a part of a fiber protein adapted to provide the chimeric adenovirus with a desired tropism to a plurality of target cells in a host". Claim 1. Claims 2 and 9 provide essentially the same element. It is inappropriate for the Office to cite the inherency in Crystal of a "particular tropism adapted for a particular plurality of target cells in a host" (Office Action,

page 8) when applicants have claimed fiber protein having desired tropism. In order for Crystal to anticipate this element of the claimed invention, it must either expressly or inherently describe fiber protein having desired tropism, not just a particular tropism. While it is true that in the entire universe of adenoviral fiber proteins, each different fiber protein will exhibit a particular tropism, it is not the case that all fiber proteins will exhibit a tropism that is desirable for a given application. This distinction is important to applicants' claimed invention and is not described in Crystal.

To make out a *prima facie* case for inherency, the burden is on the Office to propound extrinsic evidence that "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999); *see also*, M.P.E.P. § 2112. The Office, in making a case for inherency, additionally "must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 U.S.P.Q. 1461, 1464 (Bd. Pat. App. & Inter. 1990). Once the Office has established a *prima facie* case for inherency, the burden shifts to the applicant to rebut inherency with evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255; *see also* Titanium Metals Corp. v. Banner, 778 F.2d 775 (Fed. Cir. 1985); M.P.E.P. § 2112.01. With all due respect, applicants assert that the Office has not carried its burden in establishing a *prima facie* case for inherency because the Office has not shown that the allegedly inherent subject matter is necessarily present in Crystal.

In support of its case for inherency, the Office relies on Dr. Havenga's Rule 132 declaration, apparently to provide a basis in fact and/or technical reasoning to support its determination that Crystal necessarily teaches adenoviral fiber proteins having desired tissue tropisms. Applicants respectfully point out that the declaration of Dr. Havenga does ***not*** support the necessary inherency in Crystal of adenoviral fiber proteins having desired tissue tropisms. Rather, Dr. Havenga's declaration is limited to the range of antigenicities in humans of the different adenovirus serotypes. The declaration makes no reference to tissue tropism. Therefore, Dr. Havenga's declaration is not relevant to the issue of tissue tropism and does not support the inherency in Crystal of fiber proteins having desired tissue tropisms.

Applicants concede that the fiber proteins of the various adenovirus serotypes play a role in providing particular tropisms for each serotype. *See, e.g.,* Specification, page 4 line 16 to page 5 line 2; Crystal, col. 3 lines 17-34. Crystal teaches that a wild-type adenovirus fiber protein can be simply replaced in its entirety with the corresponding fiber protein of a different adenovirus serotype, or a nonnative fiber protein can be created by effecting deletions, insertions, and mutations in the wild-type fiber protein. *See, e.g.,* Crystal, col. 11 lines 56-62, col. 28 lines 1-8. Crystal's manipulation of wild-type adenoviral fiber proteins results in chimeric adenoviruses that have nonnative fiber proteins, thereby providing the chimeric adenovirus with nonnative tissue tropism. However, Crystal fails to teach anything more specific than nonnative fiber proteins. The chimeric adenoviral fiber proteins of Crystal potentially can have desired tissue tropisms, but that is nothing more than a possibility in the context of Crystal's claims.

This uncertain possibility is insufficient to form the basis of a *prima facie* case for inherency. As the Federal Circuit has stated: "Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of

circumstances is not sufficient." In re Robertson, 169 F.3d at 745. To date, the Office has done nothing more than assert that it is possible in the context of the claims of Crystal to have a fiber protein that anticipates those of the present invention. Because the Office has failed to show that the chimeric adenoviral fiber proteins of Crystal necessarily, not just possibly, anticipate the presently claimed fiber proteins having desired tropism, the Office has not established a case for inherency of the cited elements in Crystal.

Clearly, a structural difference exists between the adenoviral fiber proteins claimed in Crystal and those claimed in the present application. Namely, Crystal sets forth every possible permutation of an adenoviral fiber protein, including completely artificial fiber protein constructs. Contrarily, the present application claims only those fiber proteins that provide desired tropism. In the context of the Crystal claims, the fiber protein potentially can exhibit desired tropism, but this sort of potential anticipation is not sufficient to establish inherency, as described above. A fiber protein having a desired tropism is necessarily structurally different from a fiber protein having an undesired tropism. Because Crystal does not distinguish between desired and undesired fiber protein tropism, it cannot be said that Crystal necessarily teaches a fiber protein having desired tropism. Therefore, Crystal does not anticipate claims 1 through 3 and 9 through 11.

Entry of Amendments

The proposed amendment to claim 2 should be entered by the Examiner because the amendment is supported by the as-filed specification and drawings and does not add any new matter to the application. Further, the amendment does not raise new issues or require further search. Finally, if the Examiner determines that the amendment does not place the application in condition for allowance, entry is respectfully requested upon filing of a Notice of Appeal herein.

Conclusion

Claims 1 through 3 and 9 through 11 are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. Should the Examiner determine that additional issues remain that might be resolved by a telephone conference, he is respectfully invited to contact Applicants' undersigned attorney.

Respectfully submitted,

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Enclosures:
- postcard acknowledging receipt of applicants' Second Supplemental Information Disclosure Statement and form PTO-1449;
- Second Supplemental Information Disclosure Statement, dated 24 January 2001; and
- Form PTO-1449, dated 24 January 2001.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

2. (Three Times Amended) A recombinant vector derived from an adenovirus comprising at least one ITR and a packaging signal having a first insertion site for a nucleic acid sequence of interest, and further having a second insertion site for functionally inserting a gene encoding a penton and/or hexon protein of a first serotype of adenovirus and having a third insertion site for a gene sequence encoding at least a [functional]part of a fiber protein of a second adenovirus of a second serotype, a gene encoding a penton and/or hexon protein from the first adenovirus serotype inserted into the second insertion site, the first adenovirus serotype less antigenic in a human than the second adenovirus serotype, a gene sequence encoding at least a [functional]part of a fiber protein of the second adenovirus serotype inserted into the third insertion site, the gene sequence encoding at least a [functional]part of a fiber protein adapted to exhibit a desired tropism to a plurality of target cells in a host.